Iron accumulation and transverse relaxation rates: A quantitative postmortem study

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1. Introduction

Iron deposition in human brain tissue occurs in the process of normal aging and increased brain iron levels are considered as a marker for various neurodegenerative diseases, including Parkinson's and Alzheimer's disease [1-2]. Current approaches of assessing iron concentrations in vivo are mainly based on relaxivity effects of iron, i.e. on changes of R_2, R_2*, or R_2' relaxation rates. However, due to the lack of a gold standard it remains unclear, which transverse relaxation rate is the most sensitive and reliable marker for iron deposition. The goal of this study was to validate R_2 and R_2* relaxation rates as sensitive and linear measures for brain iron concentrations. Therefore, postmortem human brains were scanned in situ and iron concentrations were then determined using inductively coupled plasma mass spectrometry (ICPMS) in several grey matter (GM) and white matter (WM) regions.

2. Subjects and Methods

Five subjects (age at death: 38-81yrs) without known neurological deficits underwent MRI at 3T (TimTrio, Siemens Healthcare, Erlangen, Germany) within 72 hours after death. Brain temperature at the start of the scan was between 4° and 7 °C. Transverse relaxation data was acquired with a spoiled FLASH sequence (TR/TE/FA=68ms/4.92ms/20°, matrix=256x208, resolution=1x1x4mm³) with 12 equally spaced echoes (spacing=4.92ms) and a dual spin echo TSE sequence ($TR/TE_1/TE_2$=5260ms/10ms/73ms, matrix=256x192, resolution=1x1x3mm³). R_2* was calculated from the multiecho data with a monoexponential fit. R_2 was estimated from the double echo data. After MRI, brains were extracted and fixed in 4% neutral buffered formalin for at least three weeks. Freeze dried specimens dissected from GM (putamen, globus pallidus, caudate nucleus, thalamus, pons) and WM (corpus callosum, frontal, temporal, occipital) were mineralized with nitric acid in a microwave heated autoclave (UltraCLAVEIII, EMLS, Leutkirch, Germany). The iron concentrations were determined with an inductively coupled plasma mass spectrometer (Agilent 7500ce, Agilent Technologies, Waldbronn, Germany) at m/z 56 in He-mode. The accuracy of the results was checked with the NIST bovine muscle (RM 8414). According to the position of the dissected tissue specimens, regions of interest were outlined manually in the TSE images. The iron concentration was then correlated with the transverse relaxation rates using linear regression analysis.

3. Results

Figures 1 and 2 illustrate the relation between transverse relaxation rates and brain iron concentrations. In GM regions iron concentrations ranged from 40 to 250mg/kg wet mass, except for the pons, where a range between 10 and 20 mg/kg wet mass was observed. Considering GM structures only, both, R_2 and R_2* showed a strong positive linear correlation with iron concentration (r^2=0.67 for R_2 and r^2=0.83 for R_2*). R_2 in GM and WM were affected differently by iron concentration (Figure 1) while R_2* was independent of the tissue type underlying (Figure 2). Iron concentrations found in WM were lower than 65mg/kg wet mass and did not significantly correlate with transverse relaxation rates.

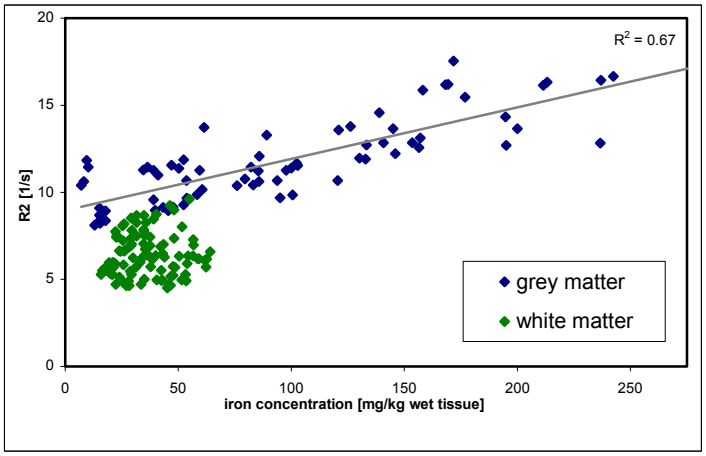

Figure 1: R_2 vs. iron concentration

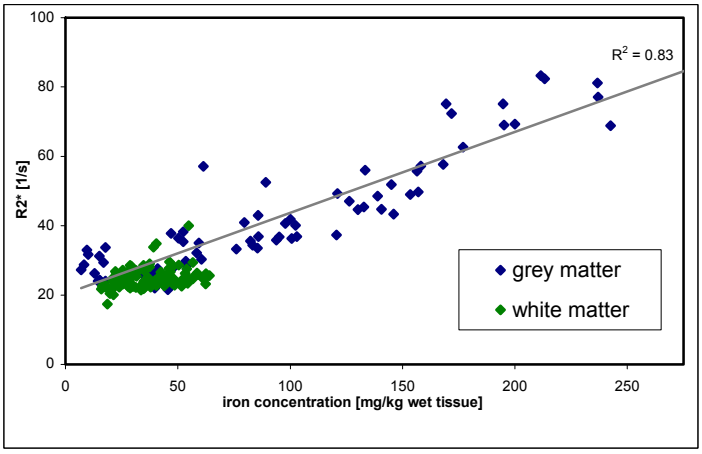

Figure 2: R_2* vs. iron concentration

4. Discussion and Conclusion

The relaxation rates found by the present study are slightly lower than previous reported rates in fixed postmortem tissue [4-5]. These differences might be caused by varying temperatures and partially by autolysis. The iron concentrations found here in postmortem brains were also in the range reported by Hallgren and Sourander [2]. In contrast to Hallgren's work, blood was maintained in the vessels during preparation for the ICPMS measurements. This represents a more realistic in vivo situation, where hem bound iron in also contributes to contrast generation. The strong correlation between R_2 relaxation rates and iron concentration confirms previous findings of basal ganglia hypointensities in T_2 weighted images [6] and suggests iron deposition as the major source for MR contrast in that region [7]. In conclusion, this study validated that due to their strong correlation with iron, both, R_2 and R_2* can be used as surrogate markers for iron deposition.

References:
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